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STEVEN L. HIGHLANDER
FULBRIGHT AND JAWORSKI
P O BOX 4433
600 CONGRESS AVE, SUITE 78701
AUSTIN,, TX 78701

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BEFORE THE BOARD OF PATENT APPEALS

AND INTERFERENCES

Application Number: 09/061,417

Filing Date: April 16, 1998

Appellant(s): OLSON ET AL.

STEVEN L. HIGHLANDER

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/20/04.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1, 4, 9 stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Gura, T. « Antisense has growing pains », Science, vol. 270, no. 27 (October 1995), pp.575-577.

Miller, N et al. « Targeted vectors for gene therapy", FASEB J., Vol. 9 (1995), pp. 190-199.

Deonarain M.P. "Ligand-targeted receptor-mediated vectors for gene delivery", Expert Opin. Ther. Pat., Vol. 8 (1998), pp. 53-69.

Verma I.M. et al. « Gene therapy-promises, problems and prospects », Nature, Vol. 389 (18 September 1997), pp. 239-242.

Crystal R.G. « Transfer of genes to humans: Early lessons and obstacles to success", Science, Vol. 270 (20 October 1995), pp. 404-410.

Haverich A. et al. "Cyclosporin A and transplant coronary disease after heart transplantation: facts and fiction", Transplantation Proceedings, vol. 26, No. 5 (October 1994), pp. 2713-2715.

Reid, C. J. et al. « Determinants of left ventricular function one year after cardiac transplantation", Br. Heart J., Vol. 59 (1988), pp. 397-402.

McCaffrey, P.G. et al. « Isolation of the cyclosporin-sensitive T cell transcription factor NFATp", Science, Vol. 262 (29 October 1993), pp. 750-754.

Martinez-Martinez S. et al. « Blockade of T-cell activation by dithiocarbamates involves novel mechanisms of inhibition of nuclear factor of activated T cells", Molecular and cellular Biology, Vol. 17, No. 11 (November 1997), pp. 6437-6447.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 1, 4, 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 4, 9 are drawn to a method for treating hypertrophy, comprising inhibiting NF-AT3 with an agent, wherein said agent inhibits NF-AT3 function in a cardiomyocyte, wherein said agent may be a small molecule inhibitor that binds to and inactivates NF-AT3.

The specification discloses that antibodies specific for NF-AT3 are able to eliminate complexes formed between BNP promoter and cardiac protein extracts (Example 4, page 75, last paragraph bridging page 76), which is presumably activated in the presence of GATA4, NF-AT3 and calcineurin (Example 4). The specification discloses that agent that reduces the expression of NF-AT3 could be an antisense construct or an antibody or a small molecule inhibitor (p.4, last paragraph). The specification also contemplates the use of a mimetic of beta-turns within GATA4, that binds to NF-AT3 in a manner analogous to the transcriptional factor GATA4, and specifically inhibits NF-AT3 binding to GATA4 (p.29).

The specification discloses two calcineurin inhibitors, cyclosporin A, and FK506, which inhibit the hypertrophic effects of AngII and PE (Example 5 on page 76), and the structure of which is known in the art.

It is noted however cyclosporin A, and FK506 are calcineurin inhibitors, and presumably **indirectly** inhibit the function of NF-AT3 via calcineurin, wherein calcineurin presumably dephosphorylates NF-AT3 in the cytoplasm of cardiomyocytes, and enabling its translocation to the nucleus, where it can interact with GATA4, resulting in up-regulation of cardiac hypertrophic genes, such as beta-naturietic peptide (BNP) (specification, page 13, first paragraph and figure 8).

There is no disclosure that cyclosporin A, and FK506 bind to NF-AT3.

It is noted that an agent that inhibits NF-AT3 function, wherein said agent may be a small molecule inhibitor that binds to and inactivates NF-AT3 encompasses numerous structurally unrelated compounds, such as a single chain antibody antagonist of NF-AT3, small antisense oligonucleotide molecules that could inhibit NF-AT3 **in vivo**, as well as GATA4 and NF-AT3 mimetics, numerous other competitive inhibitors of NF-AT3, such as numerous other peptides and non-peptide molecules that bind to and inhibit NF-AT3.

Except for a single chain antibody antagonist of NF-AT3 disclosed in the specification, and two calcineurin inhibitors, cyclosporin A, and FK506 (Example 5 on page 76), which are known in the art, and which however are not disclosed as binding to NF-AT3, the structure of which small antisense oligonucleotide molecules that could inhibit NF-AT3 **in vivo**, as well as GATA4 and NF-AT3 mimetics, numerous other

competitive inhibitors of NF-AT3, such as numerous other peptides and non-peptide molecules that bind to and inhibit NF-AT3 is not disclosed in the specification, nor in the art, nor said structure could be predicted.

There is no suggestion in the specification of how such NF-AT3 inhibitor compounds could be made or otherwise obtained other than by trial-and-error. Further, no three dimensional structure of GATA4 or NF-AT3 is disclosed in the specification, nor in the art.

It is noted that in a recent 2004 court case (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) recited by Appellant, the court states that "even with the three dimensional structure of enzymes such as COX-1 and COX-2 in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them".

The present application is similar to that in Rochester case, in that although the structure of GATA4 or NF-AT3 is known in the art, and except for antibody inhibitor of NF-AT3, one cannot predict what competitive inhibitors of NF-AT3, what mimetics of GATA4 or NF-AT3, or which small antisense compounds might bind to and inactivate NF-AT3 **in vivo**, especially in view that three dimensional structure of GATA4 or NF-AT3 is not even disclosed in the specification or known in the art, and in view that antisense therapy is unpredictable, as taught by Gura et al (see below discussion of antisense therapy under 112, first paragraph, scope of enablement rejection on pages 14-15).

The recitation of a single chain antibody against NF-AT3 (p.28, last paragraph bridging p.29), and two calcineurin inhibitors, cyclosporin A, and FK506, which however are not disclosed as binding to NF-AT3, would not be a representative number of species of small molecule inhibitors that bind to and inactivate of NF-AT3, in view that the disclosed single chain antibody against NF-AT3 and two calcineurin inhibitors, cyclosporin A, and FK506, do not have any structural relationship with each other, nor with the claimed NF-AT3 inhibitors, which encompass numerous molecules such as single chain antibodies, numerous mimetic peptides other than antibodies, antisense oligonucleotides, and numerous other competitive inhibitors of NF-AT3, such as other peptides and non-peptide molecules that bind to and inactivate NF-AT3, and further in view that no common structure of the claimed NF-AT3 inhibitors is disclosed in the specification, nor is it known in the art.

Another recent court case, *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), which although drawn specifically to the DNA art, is clearly relevant to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA..."requires

a precise definition, such as by structure, formula, chemical name, or physical properties", not a mere wish or plan for obtaining the claimed chemical invention".

The instant disclosure of an anti-NF-AT3 antibody, and two calcineurin inhibitors, cyclosporin A, and FK506, does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera having diverse structure.

The instant specification fails to provide sufficient descriptive information, such as definitive common structural features of the claimed NF-AT3 inhibitors. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Furthermore, although molecular modeling is known in the art, the structure of the claimed mimetics or small molecule inhibitors is not known. The prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the encompassed NF-AT3 inhibitor molecules and no identifying characteristic or property of the instant NF-AT3 inhibitor molecules is provided such that one of skill would be able to predictably identify the encompassed NF-AT3 inhibitor molecules, as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, and further because the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus, the disclosure of an anti-NF-AT3 antibody , and two calcineurin inhibitors,

cyclosporin A, and FK506, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Thus, only a method for treating cardiac hypertrophy in a cardiomyocyte cell, comprising exposing to said cell an antibody that inhibits NF-AT3 function, but not the full breadth of the claims meet the written description provisions of 35 USC 112, first paragraph.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE OF ENABLEMENT

Claims 1, 4, 9 are rejected under 35 USC 112, first paragraph, because the specification, while being enabling for a method for treating cardiac hypertrophy, comprising inhibiting NF-AT3 with an agent that binds to and inactivates NF-AT3, wherein said agent is an antibody, does not reasonably provide enablement for a method for treating hypertrophy, comprising inhibiting NF-AT3 with an agent, wherein said agent inhibits NF-AT3 function in a cardiomyocyte, wherein said agent may be a small molecule inhibitor that binds to and inactivates NF-AT3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1, 4, 9 are drawn to a method for treating hypertrophy, comprising inhibiting NF-AT3 with an agent, wherein said agent inhibits NF-AT3 function in a cardiomyocyte, wherein said agent may be a small molecule inhibitor that binds to and inactivates NF-AT3.

The specification discloses that antibodies specific for NF-AT3 are able to eliminate complexes formed between BNP promoter and cardiac protein extracts (Example 4, page 75, last paragraph bridging page 76), which is presumably activated in the presence of GATA4, NF-AT3 and calcineurin (Example 4). The specification discloses that agent that reduces the expression of NF-AT3 could be an antisense construct or an antibody or a small molecule inhibitor (p.4, last paragraph). The specification contemplates the use of mimetics as small molecule inhibitors that specifically inhibit NF-AT3 protein activity or binding to GATA4, and that said molecule may be sterically similar to the actual target compounds, at least in key portions of the target's structure and or organochemical in structure (p.29, paragraph before last). The specification also discloses that the C-terminal portion of NF-AT3 interacts with the second zinc finger of GATA4 (p.13, third paragraph, p.74, second and third paragraph). The specification discloses that peptide mimetic technology is known in the art (p.29, third paragraph).

The specification discloses two calcineurin inhibitors, cyclosporin A, and FK506, which inhibit the hypertrophic effects of AngII and PE (Example 5 on page 76), the structure of which is known in the art.

It is noted however cyclosporin A, and FK506 are calcineurin inhitors, wherein calcineurin presumably dephosphorylates NF-AT3 in the cytoplasm of cardiomyocytes, and enabling its translocation to the nucleus, where it can interact with GATA4, resulting in up-regulation of cardiac hypertrophic genes, such as beta-naturietic peptide (BNP) (specification, page 13, first paragraph and figure 8).

There is no disclosure that cyclosporin A, and FK506 bind to NF-AT3.

It is further noted that there is no disclosure concerning the **configuration** of the second zinc finger of GATA4 or of the C-terminal portion of NF-AT3. There is no disclosure of how to make the claimed GATA4 mimetics, other than a mere disclosure that the claimed mimetics may be "sterically" similar to the actual target compound.

In addition, it is noted that an agent that inhibits NF-AT3 function, wherein said agent may be a small molecule inhibitor that binds to and inactivates NF-AT3 encompasses numerous structurally unrelated compounds, such as a single chain antibody antagonist of NF-AT3, small antisense oligonucleotide molecules that could inhibit NF-AT3 **in vivo**, as well as GATA4 and NF-AT3 mimetics, numerous other competitive inhibitors of NF-AT3, such as numerous other peptides and non-peptide molecules that bind to and inhibit NF-AT3.

Except for a single chain antibody antagonist of NF-AT3, and two calcineurin inhibitors, cyclosporin A, and FK506 (Example 5 on page 76), which are known in the art, and which however are not disclosed as binding to NF-AT3, the structure of which small antisense oligonucleotide molecules that could inhibit NF-AT3 **in vivo**, as well as GATA4 and NF-AT3 mimetics, numerous other competitive inhibitors of NF-AT3, such as numerous other peptides and non-peptide molecules that bind to and inhibit NF-AT3 is not disclosed in the specification, nor in the art, nor said structure could be predicted.

There is no suggestion in the specification of how such NF-AT3 inhibitor compounds could be made or otherwise obtained other than by trial-and-error. Further,

no three dimensional structure of GATA4 or NF-AT3 is disclosed in the specification, nor in the art.

One could not extrapolate the teaching of the specification to the claims for the following reasons:

A. Concerning GATA4 mimetics, although mimetic technology is known in the art, and although one would not doubt that GATA4 does indeed bind to NF-AT3, nor would they challenge the notion that interference with that interaction will have inhibitory effects on NF-AT3 ability to activate gene transcription of hypertrophic genes, however without the knowledge of the configuration of the second zinc finger of GATA4, a site for binding of GATA4 to NF-AT3, **one would not know how to make the claimed GATA4 mimetics, other than by trial and error**, especially in view of a mere disclosure in the specification that the claimed mimetics may be "sterically" similar to the actual target compound.

Similarly, although mimetic technology is known in the art, one would not know how to make other peptides or non-peptide mimetics of NF-AT3 for use in the claimed method, other than by trial and error.

In addition, it is unpredictable that the claimed mimetics could be used successfully *in vivo* for treating cardiac hypertrophy. The claimed mimetics must accomplish several tasks to be effective. They must be delivered into the circulation and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. It is clear, as disclosed above that the specification does not teach how to make/use a formulation with a targeting molecule. In addition variables

such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The formulation may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the formulation. In addition, the formulation may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the formulation has no effect, circulation into the target area may be insufficient to carry the formulation and a large enough local concentration may not be established.

B. Concerning using an antisense molecule for the claimed method, **the claimed method encompasses gene therapy using antisense**. It is well known in the art however antisense therapy is unpredictable. As drawn to transgenic mice, in the field of antisense technology, according to Gura (Science, 1995, 270:575-577), researchers have many concerns. Gura discloses that "the biggest concern is that antisense compounds simply don't work the way researchers once thought they did." Other drawbacks in animal studies include difficulty getting antisense oligonucleotides to target tissues and the existence of potentially toxic side effects such as increased blood clotting and cardiovascular problems (page 575, col 1, para 2). Another problem stems from the fact that oligonucleotides used as controls produced the same biological effects in cell culture as did the antisense compounds (page 576, col 1, para 2 and 3). In addition, Gura reports problems with synthetic antisense oligonucleotides in that unwanted and sometimes lethal side effects occurred in animal experiments, and that

they block cell migration and adhesion to underlying tissue in vitro (page 576, col 3, para 1 and 3).

Thus a high degree of unpredictability is associated with the use of antisense constructs employed in methods of inhibiting expression of a particular protein in an animal model.

Further, the state of the art at the time of filing was that the combination of vector, promoter, protein, cell, target tissue, level of expression and route of administration required to target the tissue of interest and obtain a therapeutic effect using gene therapy was unpredictable. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of

vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

The specification provides insufficient guidance with regard to these issues and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success.

It is noted however that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the unpredictability of the structure of the claimed NF-AT3 inhibitors, for use in the claimed method of treating hypertrophy, the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

REJECTION UNDER 35 USC 102(b)

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Haverich, A et al, 1994, or Ried, CJ et al, 1988.

Claim 1 is drawn to a method of treating hypertrophy in a subject, comprising the step of inhibiting the function of NF-AT3 in a cardiomyocyte, wherein inhibition of NF-AT3 function inhibits hypertrophic gene expression, thereby treating hypertrophy.

Claim 1 reads on a method of treating hypertrophy in a subject, comprising the step of inhibiting the function of NF-AT3 in a "cardiomyocyte", using a compound that inhibits the function of NF-AT3.

It is noted that claim 1 does not recite a method of treating "cardiac" hypertrophy. Further, claim 1 does not require that the inhibition of NF-AT3 is by an agent that binds to and inactivates NF-AT3. In addition, there is no active step other than inhibiting the function of NF-AT3 in a cardiomyocyte in claim 1. There is no requirement in claim 1 that the treated cardiomyocyte is the cardiomyocyte of a subject having cardiac hypertrophy.

Haverich, A et al teach treating of transplant coronary disease, comprising administering cyclosporin A.

Reid et al teach treating patients with cardiac transplantation cyclosporin A (p.399, first column, under immunosuppression).

Although Haverich, A et al and Reid et al do not teach cardiomyocytes, it is well known in the art that the heart comprises cardiomyocytes, which are inherently exposed to cyclosporin A in the method of Haverich et al or Reid et al.

McCaffrey, PG et al teach that cyclosporin A blocks the dephosphorylation of NFATp and the appearance of NFAT in nuclear extracts (p.750, second column, last paragraph bridging third column).

Martinez-Martinez, S et al teach that cyclosporin A inhibits NFATp by preventing the dephosphorylation and translocation into the nucleus of NFATp, which comprises NFAT1, NFATc and NFAT3 (p.6437).

In other words, cyclosporin A is an inhibitor of NFAT3, and it is clear that the administered cyclosporin A taught by the art would inhibit the function of NF-AT3 in a cardiomyocyte.

Because the method of the prior art comprises the same method step as claimed in the instant invention using the same composition, i.e. a compound that inhibits the function of NF-AT3, the claimed method is anticipated because the method will inherently lead to the claimed effects. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

(11) Response to Argument

A. Standard of review

Appelant asserts that findings of facts and conclusions of law must be made in accordance with the Administrative Procedure Act, 5 USC 706(A), (E), 1994, *Dickinson v. Zurko*, 527 US 150, 158 (1999). Appelant recites case law, stating that findings of fact by the Board of Patent Appeals and Interferences must be supported by "substantial evidence" within the record and that accordingly, an Examiner's position on Appeal must be supported by "substantial evidence" within the record in order to be upheld by the Board of Patent Appeals and Interferences.

The recitation of standard of review is acknowledged.

B. REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Appellant admission that the affidavits of Bush, Williams and Rosethermal submitted on July 09, 2003 were incorrectly filed and not relevant to the arguments herein is acknowledged.

Rejection under 35 USC 112, first paragraph of claims 1, 4, 9 pertaining to lack of a clear written description of a NF-AT3 inhibitor, wherein said inhibitor may be a small molecule inhibitor that binds to and inactivates NF-AT3, for use in the claimed method of treating hypertrophy, remains for reasons already of record.

Appellant argues that the examiner primarily cites to the Lilly case for the proposition that "an adequate written description of a DNA requires a precise definition" Appellants submit that the examiner is attempting to create a rule of law from Lilly where none currently exists. Appellant argues that Lilly and its subsequent cases have not required that an invention must **always** (emphasis added) be specifically described as

Lilly required for those particular DNA molecules, nor do the cases require that a genus must be described in its entirely.

Appellant's argument is based on mis-interpretation of the Examiner's quotation of Lilly case, and thus is not found to be persuasive. The Examiner did not recite that Lilly requires that an invention must **always** (emphasis added) be specifically described as Lilly required for those particular DNA molecules, nor that the case requires that a genus must be described in its entirely.

Rather the Examiner recited in the Office action of 07/17/01, on page 4, that "Although drawn specifically to the DNA art, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly relevant to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA..."requires a precise definition, such as by structure, formula, chemical name, or physical properties", not a mere wish or plan for obtaining the claimed chemical invention".

In the Office action of 03/18/04, the Examiner quotes Fiers, 984 F.2d at 1171, "The following teaching in the court clearly applies to the claimed invention. The court has held that statements in the specification describing the functional characteristics of

a DNA molecule or methods of its isolation do not adequately describe a particular claimed DNA sequence. Instead "an adequate written description of DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1566-67 (quoting Fiers, 984 F.2d at 1171).

Appellant argues that the Lilly situations are not presented in the case at hand, and the Examiner's attempt to broadly extend Lilly to other scenarios when the invention is described through other terms or examples is not appropriate.

Appellant argues that the important point of both Lilly and Enzo cases is that function alone cannot support a set of claims to the molecules behind that function. Appellant argues that however, the present specification does not rely on function alone. Appellant argues that specific examples and specific molecules are given in the specification.

This is not found to be persuasive. The recitation of three specific molecules, a single chain antibody against NF-AT3 (p.28, last paragraph bridging p.29), and two calcineurin inhibitors, cyclosporin A, and FK506, which are not disclosed as binding to NF-AT3, would not be a representative number of species of small molecule inhibitors that bind to and inactivate NF-AT3, because they do not share a common structural feature with each other, and because the specification does not disclose common structural features among the claimed NF-AT3 inhibitors. A generic statement in the specification of a class of compounds with a common function, without disclosure of a representative number of species or common structural features among the claimed

genus is not sufficient to meet the written description requirement, and one would conclude that the claimed invention did not have possession of the claimed NF-AT3 inhibitors at the time the invention was made.

Concerning the examiner comments that the configuration of the second zinc finger of GATA4 is not known and that specific structures are not disclosed in the specification for GATA4 mimetics, antisense molecules, or competitive inhibitors of NF-AT3 are not disclosed in the specification, Appellant argues that knowledge of the actual binding sites and exhaustive listing of structures are not a requirement for written description. Appellant asserts that as discussed in the Declaration by Dr. Rick Gorczynski (Exhibit E) that those of skill in the art would not doubt that GATA4 does indeed bind to NF-AT3, nor would they challenge the notion that interference with that interaction will have an inhibitory effects on NF-AT3's ability to activate gene transcription of hypertrophic genes, such interference clearly being mediated by any of the molecules or agents listed above or referred in the specification.

Appellant argues that the specification goes beyond simply claiming an undescribed molecule, it actually refers to GATA4 mimetics, DTC's, antisense molecule (p27, lines 12-20), antibodies, competitive inhibitors of NF-AT3 (p.30, line 21), as well as other proteins that inhibit NF-AT3 (Summary on page 4, lines 15-25, and Examples 3, 6-9). Appellant argues that these examples describe specific molecules known in the art, whose mention alone should be sufficient to satisfy the written description requirement.

Appellant further argues that the structure of GATA4 mimetics, and antisense molecules are defined by the prior art structures of the target molecules.

Appellant argues that Appellant is unaware that commonly structure is required for claiming a genus of inhibitors.

Appellant recites the Rochester case law. Appellant argues that current claims call out methods of treatment by inhibiting NF-AT3 and the specification then describes both in words and examples a variety of ways to accomplish the claimed method.

Appellant's arguments have been considered but are not deemed to be persuasive for the following reasons:

It is noted that page 27, lines 12-20 in the specification of the instant application does not recite GATA4 mimetics, DTC's, antisense molecule. The specification does not recite DTC's, which was only recited in one of the previous response to the Office action. The specification contemplates the use of mimetics of beta-turns within GATA4, that binds to NF-AT3 in a manner analogous to the transcriptional factor GATA4, and specifically inhibits NF-AT3 binding to GATA4 (p.29, lines 13-25).

However, no disclosure of structure of any GATA4 mimetics is found in the specification.

Further, although the structure of NF-AT3 is known in the art, the structure of the particular small antisense molecules that inhibit **in vivo** function of NF-AT3 is not disclosed in the specification.

Similarly, except for recitation of a single chain antibody against NF-AT3 (p.28, last paragraph bridging p.29), and two calcineurin inhibitors, cyclosporin A, and FK506

(Example 5 on page 76), which are known in the art, and which however are not disclosed as binding to NF-AT3, the structure of numerous other competitive inhibitors of NF-AT3 (p.30, line 21), as well as numerous peptides that **bind** to and inactivate NF-AT3 is not disclosed in the specification.

The recitation of a single chain antibody against NF-AT3 (p.28, last paragraph bridging p.29), and two calcineurin inhibitors, cyclosporin A, and FK506, which are not disclosed as binding to NF-AT3, would not be a representative number of small molecule inhibitors that **bind to** and inactivate of NF-AT3, because the recited single chain antibody against NF-AT3 and two calcineurin inhibitors, cyclosporin A, and FK506 do not have any structural relationship with each other, nor with the claimed inhibitors of NF-AT3, which encompass molecules such as single chain antibodies, as well as numerous mimetics other than antibodies, antisense oligonucleotides, and other competitive inhibitors such as peptides and non-peptide molecules that bind to and inactivate NF-AT3, and because no common structure of the claimed NF-AT3 inhibitors is disclosed in the specification, nor is it known in the art.

It is noted that the court stated that:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by. function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in

> the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406.

There is no suggestion in the specification of how such NF-AT3 inhibitor compounds could be made or otherwise obtained other than by trial-and-error. No three dimensional structure of GATA4 or NF-AT3 is disclosed in the specification, nor in the art.

Concerning GATA4 mimetics, and the Declaration of by Dr. Rick Gorczynski (Exhibit E), although one would not doubt that GATA4 does indeed bind to NF-AT3, nor would they challenge the notion that interference with that interaction will have inhibitory effects on NF-AT3 ability to activate gene transcription of hypertrophic genes, however without the knowledge of the configuration of the second zinc finger of GATA4, a site for binding of GATA4 to NF-AT3, **one cannot predict the structure of the claimed GATA4 mimetics.**

It is noted that in a recent 2004 court case cited by Appellant (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004), the court states that "even with the three dimensional of enzymes such as COX-1 and COX-2 in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them".

The present application is similar to that in Rochester case, in that although the structure of GATA4 or NF-AT3 is known in the art, and except for antibody inhibitor of NF-AT3, one cannot predict what competitive inhibitors of NF-AT3, what mimetics of GATA4 or NF-AT3, or which antisense compounds might bind to and inactivate NF-AT3 **in vivo**, especially in view that three dimensional structure of GATA4 or NF-AT3 is not even disclosed in the specification or known in the art.

Similarly, although small antisense molecules that inhibit NF-AT3 in vitro could be routinely screened in vitro, which small antisense molecules that inhibit NF-AT3 in vivo could not be predicted, in view of the unpredictability of antisense treatment in vivo, as taught by Gura et al.

Thus the instant application does not meet the 112, first paragraph, written description requirement. The specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

The example of Lilly is applicable to the instant application, because the recitation of a single chain antibody against NF-AT3 (p.28, last paragraph bridging p.29), and two calcineurin inhibitors, cyclosporin A, and FK506, which however are not disclosed as binding to NF-AT3, would not constitute an adequate representative number of species of small molecule inhibitors that bind to and inactivate NF-AT3, supra, and because there is no disclosure of common structural attributes among the claimed NF-AT3 inhibitors.

Thus, although knowledge of the actual binding sites and exhaustive listing of structures are not a requirement for written description, however, the recitation of a single chain antibody against NF-AT3 (p.28, last paragraph bridging p.29), and two calcineurin inhibitors, cyclosporin A, and FK506, which however are not disclosed as binding to NF-AT3, does not constitute an adequate representative number of species of small molecule inhibitors that bind to and inactivate NF-AT3, supra, and in view that there is no disclosure of common structural attributes among the claimed NF-AT3 inhibitors, one would conclude that the claimed invention did not have possession of the claimed NF-AT3 inhibitors at the time the invention was made.

Further, the instant specification does not meet the written description requirement, in view that the example of Enzo is applicable to the instant application, because the specification does not show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

Thus, the specification does not provide an adequate written description of the claimed NF-AT3 inhibitors, that is required to practice the claimed invention.

Since the specification fails to adequately describe the product for use in the claimed method, it also fails to adequately describe the claimed method of treating hypertrophy.

C. REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Claims 1, 4, 9 remain rejected under 35 USC 112, first paragraph, because the specification, while being enabling for a method for treating cardiac hypertrophy, comprising inhibiting NF-AT3 function, with an agent that binds to and inactivates NF-AT3, wherein said agent is an antibody, does not reasonably provide enablement for a method for treating hypertrophy, comprising inhibiting NF-AT3 with an agent, wherein said agent inhibits NF-AT3 function in a cardiomyocyte, wherein said agent may be a small molecule inhibitor that binds to and inactivates NF-AT3, for reasons of record.

Appellant argues that the Examiner's criticism seems to rise to the level of working model. Appellant recites MPEP 2164.02 and *In re Robins*, arguing that working examples will not by itself render the invention non-enabled. Appellant argues that a single example of in vivo proof that the use of NF-AT3 inhibitors can be a method for treating hypertrophy is adequate (Example 6 and 9). Appellant argues that the specification describes the mimetic technology, and thus it is not required to make something that is readily understood by one of skill in the art.

This is not found to be persuasive. Although the specification discloses in Example 5 that cyclosporin A and FK506 inhibit the hypertrophic effect of AngII or PE, it is noted that cyclosporin A and FK506 acts by inhibiting calcineurin, and there is no disclosure in the specification that cyclosporin A and FK506 **bind to** and inactivate NF-AT3, and thus cyclosporin A and FK506 would not be representative of the claimed small molecule inhibitors that bind to and inactivate NF-AT3. Further, the recited single chain antibody against NF-AT3, cyclosporin A and FK506 would not have any structural relationship with the claimed NF-AT3 inhibitors, which encompass single chain

antibodies, as well as numerous mimetics other than antibodies, antisense oligonucleotides, and other competitive inhibitors such as peptides and non-peptide molecules that bind to and inactivate NF-AT3, the structure of none of which is disclosed in the specification.

Further, although the mimetic technology is known in the art, obtaining successful mimetics of GATA4 or NF-AT3 that bind to and inactivate NF-AT3 would be only by trial-and-error, especially no three dimensional structure of GATA4 or NF-AT3 is disclosed in the specification, nor in the art.

In addition, in view that antisense therapy is unpredictable, as taught by Gura et al, one cannot predict which small antisense oligonucleotide would inactivate the function of NF-AT3 **in vivo**.

In view of the above, one would not known how to make the claimed NF-AT3 inhibitors, for use in the claimed method of treating hypertrophy.

Concerning Appellant's comment that the Examiner requires a working example, although a working example is not always required, it is noted however that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly

stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the unpredictability of the structure of the claimed NF-AT3 inhibitors, for use in the claimed method of treating hypertrophy, the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Appellant argues that the reference of Gura recited by the Examiner is in 1995, whereas the Bennett reference recited by Applicant is in 1998. Appellant asserts that the Examiner is convinced that the language "potentially " in the statement by Bennett, 1998, that it is possible to utilize antisense oligonucleotides as effective research tools and "potentially" as therapeutic agent, supports the Examiner case that antisense is non-enabled technology, and ignores the explicit teaching of the reference that antisense is a viable and utilizable technology.

This is not found to be persuasive. It is noted that Appellant distorts the Examiner position. The Examiner did not recite that the antisense technology is not enabled, but rather the antisense technology is an unpredictable field, despite there is successful use of antisense in some circumstances, in view of the teaching of Gura et al. Although some successful antisense treatment in certain cases is recited in Bennett et al, in 1998, this does not refute the fact that antisense technology is unpredictable, as taught by Gura in 1995.

Thus since the claims encompass use of antisense in gene therapy for treating hypertrophy, and since antisense technology is unpredictable as taught by Gura et al, and further since gene therapy is also unpredictable, as taught by Miller et al,1995, Deonarian et al, 1998, a similar date as the date of Applicant's recited Bennett et al, 1998, Verma et al, 1997, and Crystal et al, 1995, it would be undue experimentation for one of skill in the art to practice the claimed method.

D. REJECTION UNDER 35 USC 102(b)

Claim 1 remains rejected under 35 USC 102(b) as being anticipated by Haverich et al, or Ried et al, for reasons already of record .

Appellant argues as follows:

Appellant asserts that every element in claim 1 is not found in any of the prior art references. Appellant argues that the Examiner misreads the claims at issue, as the Examiner asserts that the method is to treatment of cardiomyocyte, when clearly claim 1 is directed to a method for treating cardiac hypertrophy.

Appellant asserts that Claim 1 teaches treatment of hypertrophy by inhibiting the function of NT-AT3 in a cardiomocyte using a compound that inhibits the function of NF-AT3. Appellant asserts that the Haverich and Reid references teach the use of cyclosporin A (CsA) for treatment of transplantation disease; they do not teach, much less suggest treatment of hypertrophy or effects on cardiac structure. Appellant asserts that they are instead directed towards improving cardiac function in a post-transplant environment. Appellant asserts that additionally, while the Mccaffrey and Martinez-Martinez references do teach that CsA is an NF-AT3 inhibitor, they do not teach the use

of an NF-AT3 inhibiting compound to treat hypertrophy. Appellant asserts that not one of these references teaches the invention, nor do the collection of them inherently predict or assert the invention.

Appellant asserts that Novitski merely states that inherent anticipation may lie, that claims are interpreted as broadly as reasonably possible, and that limitations are not read into the claims. Appellant asserts that however, a limitation of the instant claims is treating cardiac hypertrophy, and thus, nothing must be read into the claims, and the claims cannot be read to exclude this limitation.

Appellant submits that the case law requires that an inherent disclosure "must be certain". Ex parte Mcoueen, 123 USPQ 37 (Bd. App. 1958). Appellant asserts that there is no evidence from the cited references that hypertrophy had been treated or even analyzed. Appellant asserts that the prior art specifically deals with transplantation disease and cardiac function after transplant in response to CsA application.

Appellant argues that transplantation disease has not and is not defined as cardiac hypertrophy, and it is possible to have one without the other, thus, there cannot be any inherency. Appellant asserts that the references do not teach a treatment for hypertrophy nor would one of skill in the art be expected to infer from these references that CsA, and subsequently NF-AT3 inhibitors, were being used to treat hypertrophy. Appellant asserts that the examiner has not even attempted to address this issue, instead merely repeating the previous rejection.

Appellant argues that the rejection must assume that hypertrophy is usually associated with transplantation disease in order for the cited references to anticipate the

use of an NF-AT3 inhibitor in treating hypertrophy and that the Examiner fails to show where the nexus between treating transplantation disease and treating hypertrophy is proven. Appellant argues that it is then further assumed by the Examiner that any drug that treat transplantation disease will by implication be treating hypertrophy, an assumption that overlooks the fact that none of the clinical references even discuss hypertrophy.

Appellant's arguments have been considered but are not deemed to be persuasive for the following reasons:

Appellant distorts the Examiner position when arguing that "the Examiner asserts that the method is to treatment of cardiomyocyte, when clearly claim 1 is directed to a method for treating cardiac hypertrophy".

It is noted that claim 1 does not recite a method of treating "cardiac" hypertrophy. Further, claim 1 does not require that the inhibition of NF-AT3 is by an agent that binds to and inactivates NF-AT3. In addition, there is no active step other than inhibiting the function of NF-AT3 in a cardiomyocyte in claim 1. There is no requirement in claim 1 that the treated cardiomyocyte is the cardiomyocyte of a subject having cardiac hypertrophy.

It is further noted that the Examiner did not assert that the claimed method is to treatment of cardiomyocyte. Rather, the Examiner position has been and is that although the art does not recite that the cited method would be effective in treating hypertrophy, however, since the art method steps are the same as the claimed method steps, i.e., inhibiting the function of NF-AT3, using the same claimed composition, i.e.,

in a cardiomyocyte, one would expect that inherently the method taught by the art would have the same effect as the claimed method.

It is noted that Novitski teaches that "Because the method of the prior art comprises the same method steps as claimed in the instant invention using the same composition, the claimed method is anticipated because the method will inherently lead to the claimed effects". See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

MINH TAM DAVIS, Ph.D

Patent Examiner

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YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Conferees

1) SPE Yvonne Eyler

2) SPE Jeffrey Siew

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
2/6/05

STEVEN L. HIGHLANDER

FULBRIGHT AND JAWORSKI

P O BOX 4433

600 CONGRESS AVE, SUITE 78701

AUSTIN,, TX 78701